Gut Microbiota Mediate Melatonin Signaling in Association With Type 2 Diabetes

Rui Lin, Xueran Hoang, Yang Qiu, Yongfen Gao, Rong Zhou, Qiantu Hu, Zouyan He, Yingnan Lv, Xi Wang, Wanrong Chen, Yuqing Deng, Zhuangzhuang An, Haiying Zhang, and Zengnan Mo

Guangxi Medical University

Objectives: To investigate the association between serum melatonin (MT) and type 2 diabetes (T2D) risk in southern Chinese population in a case-control study as well as the role of gut microbiota in the relationship between them.

Methods: T2D cases and healthy controls (n = 2034) were recruited from a cross-sectional study and matched age and sex for a case-control study, and the association between serum MT and T2D risk was examined using a multivariable logistic regression model. We further conducted a rigorously matched case-control study (n = 120), in which gut microbial 16S RNA was sequenced and metabolites were profiled using an untargeted LC-MS/MS approach.

Results: Higher levels of serum MT were significantly associated with a lower risk of T2D (OR = 0.84; 95% CI 0.75–0.93) and with lower levels of fasting glucose after adjustment for covariates (β = −0.21; 95% CI −0.33, −0.09). T2D patients exhibited lower levels of serum MT, lower α- and β-diversity of gut microbiota ($p < 0.05$), greater abundance of *Bifidobacterium* and lower abundance of *Coprococcus* (LDA > 2.0). Seven genera were correlated with MT and T2D related traits, among them *Bifidobacterium* was positively correlated with serum LPS and IL-10, whereas *Coprococcus* was negatively correlated with serum IL-1β, IL-6, IL-10, IL-17, INF-α and LPS (FDR < 0.05). Moreover, altered metabolites were detected in the T2D patients, and there was a significant correlation between tryptophan (Trp) metabolites and the melatonin-correlated genera including *Bifidobacterium* and *Coprococcus* (FDR < 0.05). A significant correlation also was found between Trp metabolites and inflammation factors, such as IL-1β, IL-6, IL-10, IL-17, INF-α and LPS (FDR < 0.05). Further, we showed that Trp metabolites may serve as a biomarker to predict T2D status (AUC = 0.804).

Conclusions: Higher level of serum MT was associated with lower risk of T2D, and that gut microbiota-mediated MT signaling was involved in this association, especially, *Bifidobacterium* and *Coprococcus* mediated Trp metabolites may be involved in the process. These findings uncover the importance of MT and MT-related bacteria and metabolites as potential therapeutic targets for T2D.

Funding Sources: This work was supported by the National Natural Science Foundation of China (No.82060593), Natural Science Foundation of Guangxi Province (No. 2018GXNSFDA050019).